Gliome – was ich wissen muss in zehn Fragen

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Abstract: Gliomas are the most common primary tumors involving the central nervous system. They can manifest with diverse and non-specific general and neurological symptoms. The diagnostic gold standard is cerebral magnetic resonance imaging and subsequent histological confirmation of the diagnosis. Steroids, especially dexamethasone, are used in case of focal symptoms and of symptoms caused by increased intracranial pressure, and antiepileptic drugs are used to manage epileptic seizures. Non-enzyme-inducing antiepileptic drugs are preferable. Glioma patients have an inherently elevated thromboembolic risk, and therapeutic anticoagulation is indicated following a thromboembolic event. Surgery, radiotherapy and systemic therapy are used as tumor-specific therapy modalities in gliomas. Molecular markers play an increasing role in the prognosis and selection of therapy in daily oncological routine.

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Other titles: Gliomas – What I Have to Know in ten Questions

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Therapy for secondary CNS involvement in malignant lymphomas: no standard yet!

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The prognosis of secondary CNS involvement in systemic lymphomas (secondary CNS lymphoma, SCNSL) is poor and the optimum treatment remains to be established. Due to the rarity of SCNSL and lack of prospective trials, the level of evidence guiding therapy is low. Limited data suggests that intensive systemic chemotherapy followed by high-dose chemotherapy and autologous stem-cell transplantation (HD-ASCT) is the only potentially curative approach.

Ferreri et al (1) report on a phase II trial of 38 patients with SCNSL treated with an anti-metabolite-based chemotherapy followed by HD-ASCT. For all patients, the 2-year event-free survival (EFS) was 50% and the 5-year EFS 41% (68% for patients completing HD-ASCT). The authors conclude that this regimen should be considered as the new standard of care for SCNSL patients. This is a well-conducted and concisely reported trial, but there are several aspects that warrant commentary.

First, the complete omission of anthracyclines and vinca alkaloids, uniformly accepted as standard therapy of aggressive B-cell lymphomas, likely led to under-treatment of chemotherapy-naïve patients, for whom R-CHOP-like protocols that include CNS penetrating drugs might be a preferable (and currently utilized) treatment option.

Second, study patients were heterogeneous with respect to histology (diffuse large B-cell n=32), mantle-cell (n=3) and indolent (n=3) lymphoma). The assumption by the authors, that histology does not impact outcome in SCNSL has never been substantiated. Moreover, both therapy-naïve patients with CNS involvement at diagnosis (n=16) and pretreated patients with SCNSL at relapse (n=22) were included, and there was a wide temporal range between time of lymphoma diagnosis and CNS involvement (0-69 months). The authors contend that outcome of SCNSL is similar regardless of histology and pretreatment. Because of the small sample size, these assumptions cannot be corroborated. For example, the difference in 5-year overall survival between patients with delayed SCNSL (45%) and SCNSL at diagnosis (36%) suggests a better prognosis for the delayed group (relative risk 1.21), however, the precision of this estimate is very low (95% confidence interval 0.56 - 2.65). Further heterogeneity and potential bias is introduced by the wide variety of previous treatments received by the 58% of patients with delayed SCNSL.

Most importantly, despite the valuable information this trial provides, it is uncontrolled, and the primary outcome measure (2-year EFS) was assessed by unblinded treating investigators. Both of these features demand the assignment of class IV evidence for this study, which can never be the basis of standard-of-care decisions. Even ignoring this important issue, the trial failed to achieve its pre-defined primary outcome (a 2-year EFS of 60%). To demonstrate a convincing treatment effect using the same primary outcome measure, all the same study parameters (significance of 0.05, power of 80%, uninteresting response rate of 40%) and the actual 2-year EFS seen in this trial (50%), 154 patients would have been required using the same Fleming design employed by the authors.

The third point is the feasibility of the proposed therapy. The authors state that the protocol was tolerable, notwithstanding the reported drop-out rate of 47% (18 of 38 patients).

Moreover, it is stated that 123 (81%) of the 152 cycles planned were administered. However, in that HD-ASCT was included as planned therapy, it appears that only 65% (123 of 190) of planned cycles were given.

The fourth point of concern is toxicity of the treatment. The toxicity-related death rate of 11% (95% confidence interval 4.2% - 24.1%) is formidable. Additionally, three patients had grade 3-4 bleeding, two had Aspergillus pneumonia, one patient each had Guillain-Barré syndrome and a secondary malignancy and an unspecified number of patients manifested cytomegalovirus reactivation. The authors state that no late neurotoxicity was seen, however, the method and timing of evaluation are not stated.

The study by Korfel et al. mentioned in the accompanying editorial (2) illustrates that a relatively homogenous group of patients with SCNSL can be recruited and treated in a prospective multicenter study (all patients had aggressive lymphoma with SCNSL at relapse and were pretreated, the majority with R-CHOP), that a chemotherapy-only regimen is feasible in patients with SCNSL and is associated with a relatively low drop-out rate (80% completed the study protocol), and that a 2-year EFS of 50% can be achieved with an acceptable therapy-related death rate of 3%.

The protocol reported by Ferreri et al. deserves further evaluation in a well-defined, more homogeneous patient population and with a predefined monitoring protocol for toxicity. Before this is done, however, considering this regimen standard for routine patient care and in the design of future studies seems premature.

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